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28 October 1997

NTP Board of Scientific Counselors' *Report on Carcinogens* Subcommittee
c/o Dr. Larry G. Hart, Executive Secretary
National Institute of Environmental Health Sciences
Research Triangle Park NC

Dear Subcommittee Members:

We the undersigned believe the proposal to upgrade 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) to *Known Human Carcinogen* status in the 9th *Report on Carcinogens* is not supported by the scientific evidence. TCDD should be left in its present classification category, *Reasonably Anticipated to be a Human Carcinogen.*

In February 1997, an IARC Working Group summarized its evaluation of the scientific evidence regarding the carcinogenic risks posed by TCDD as follows:

> "There is *limited evidence* in humans for the carcinogenicity of 2,3,7,8-tetrachloro-dibenzo-*para*-dioxin."
>
> "There is *sufficient evidence* in experimental animals for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin."

The IARC Monographs Preamble describes *limited evidence* in humans as follows:

> "A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interprestion is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."

In comparison, the *Report on Carcinogens* criterion for listing a substance as a *Known Human Carcinogen* is:

> "There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer."

Presuming the accuracy of the IARC Working Group's evaluation, the evidence for the carcinogenicity of TCDD in humans falls short of satisfying this criterion. We are aware of no evidence, be it epidemiologic, toxicologic, or mechanistic, that would justify upgrading the *Report on Carcinogens* classification of TCDD to a *Known Human Carcinogen* at the present time.

We realize that the IARC Working Group placed TCDD in IARC's Group 1 (carcinogenic to humans) based on 1) the sufficiency of evidence for the carcinogenicity of TCDD in experimental animals, 2) the presence and similarity of function of the evolutionarily conserved Ah receptor in humans and experimental animals, and 3) the similarity of TCDD tissue concentrations in heavily exposed human populations in which an increased overall cancer risk was observed to those in rats exposed to carcinogenic doses in bioassays.

We agree with the Working Group's assessment that the evidence for the carcinogenicity of TCDD in experimental animals is sufficient. However, this evidence is not sufficient to classify TCDD as a *Known Human Carcinogen*, and we do not find the additional lines of evidence regarding the Ah receptor and TCDD tissue concentrations at all compelling with regard to the potential human carcinogenicity of TCDD.

Consider first the scientific evidence regarding the Ah receptor. Its role in the production of biochemical and toxic responses to TCDD exposure has been characterized fairly as *necessary but not sufficient.* Thus, its presence and similarity of function across species do not guarantee a similarity of responses, either biochemical or toxic. At the present time, it is impossible to predict what, if any, toxic response might occur in a specific tissue in any given species solely on the basis of Ah receptor presence and functionality. Indeed, a remarkable *disparity* in responses to TCDD exposure exists across tissues and species, yet the mechanisms underlying these marked response differences are multiple, and not known or characterized with any degree of scientific certainty (c.f., the review by Schmidt and Bradfield, *Annu Rev Cell Dev Biol* 12:55-89, 1996). Ah receptor occupancy by TCDD is just one, albeit very important, early step in a multiple pathway web of interactions that may, or may not, in any given situation, lead to a toxic response. Lack of understanding of the complex molecular events downstream from receptor occupancy that might or might not culminate in malignancy prevents one from concluding on mechanistic grounds that TCDD is a *known human carcinogen* at the present time.

Next, consider the evidence regarding the similarity of TCDD tissue concentrations (i.e., esitmated body burdens) in heavily exposed human populations to those in rats exposed to carcinogenic TCDD doses. While elevated cancer risks have been reported in studies of some heavily exposed human populations, the IARC Working Group was unable to confidently rule out chance, bias or confounding as being responsible for them. This means that TCDD exposure might not have been the cause of the reported excess risks. If the excess risks were in fact due to factors other than heavy TCDD exposure, then this evidence shows only that certain heavily exposed human populations developed TCDD body burdens similar to those in rats that received carcinogenic bioassay doses. It shows nothing about the actual carcinogenicity of TCDD in humans.

In summary, the scientific evidence is not sufficient at present to conclude that TCDD is a *Known Human Carcinogen.* We encourage the Subcommittee to leave TCDD in its current *Report on Carcinogens* category, namely, ***Reasonably Anticipated to be a Human Carcinogen.***

Sincerely,

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